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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,466	09/05/2007	Stephen Jay Anderson	GNE-5201 (24126.286)	3697

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,466	ANDERSON ET AL.	
	Examiner	Art Unit	
	WU-CHENG SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *272,273,280-284 and 291* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *272,273,280-284 and 291* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2010 has been entered

Claims 1-271, 274-279, 285-290 and 292-386 are cancelled. Claims 272, 273, 280 and 291 are amended.

Claims 272, 273, 280-284 and 291 are pending.

Claims 272, 273,280-284, and 291 are currently under examination to the extent of a phenotype is a retinal abnormality, which is a species belongs to the genus of eye abnormality.

This application 10/583,466 is a 371 of PCT/US04/41721 12/13/2004 which claims benefit of 60/530,043 filed on12/16/2003.

Claim Objections

1. Previous objection of claim 273 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is **withdrawn** because claim 273 has been amended to recite "eye abnormality is a retinal abnormality comprising retinal artery obstruction or occlusion".

2. Previous objection of claim 272 is objected to because of the recitation of"PR0224" is **withdrawn** because the claim has been amended to recite "PRO224".

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Previous rejection of claims 272, 273, 280-284, and 291 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** because the claim 272 has been amended and no longer recites a broad recitation "a phenotype" in step(c), and narrower statement of the range/limitation "an eye abnormality" in step (e).

4. Claims 281, 282 and 284 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 280 is directed to the method of claim 272, wherein the eye abnormality is a retinal abnormality.

Claim 281 is directed to the method of claim 280, wherein the eye abnormality is a retinal abnormality consistent with vision problems or blindness.

Claim 282 is directed to the method of Claim 280, wherein the retinal abnormality is consistent with retinitis pigmentosa.

Claim 284 is directed to the method of claim 280, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma,

hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysaria congentia, Flynn-Aird syndrome, Fried_reich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Keams- Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemeia, cystinosis, Wolfram syndrome, Bassen-Komzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopoly-saccharidoses, homocystinuria, or mannosidosis.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App. 1961); Ex parte Hall, 83 USPQ 38 (Bd. App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949). In the present instance, the phrase "consistent with" recited in claims 281, 282, and 284 render the metes and bounds of limitation "retinal abnormality"

unclear. For instance, the phrase "consistent with" recited in claim 281 encompasses the scenario that "retinal abnormality" is the cause that results in the effect of "vision problems or blindness". Accordingly, claim 281 simultaneously recites a more narrow limitation "retinal abnormality" and a much broader limitation "vision problems or blindness". The same interpretation of the phrase "consistent with" applies to claims 282 and 284

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Previous written description rejection of claims 272, 273, 280-284, and 291 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is **withdrawn** because the limitation "the gene that encodes for a native sequence PR0224 polypeptide" has been amended in the context of "transgenic mouse whose genome comprises a disruption of the gene that encodes for a native sequence PR0224 polypeptide"

6. Previous total lack of enablement rejection of claims 272, 273, 280-284, and 291 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as the claim(s) contains subject matter, which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is **withdrawn** because the claims have been amended.

Amended claim 272 filed on 10/29/2010 reads as follows: A method of identifying an agent that modulates an eye abnormality, the method comprising: (a) providing a transgenic mouse whose genome comprises a disruption of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the transgenic mouse of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type mouse, wherein the physiological characteristic of an eye of the transgenic mouse that differs from the physiological characteristic of the wild-type mouse is identified as an eye abnormality resulting from the gene disruption in the transgenic mouse; (d) administering a test agent to the transgenic mouse of (a); and (e) determining whether the test agent modulates said eye abnormality, whereby an agent which is determined to modulate an eye abnormality is identified.

Applicant provides the following statements on page 11 of Applicant's reply filed on 10/29/2010.

"Citing Upton et al., the USPTO is concerned that there allegedly may not be a "clear association" between a phenotype of a retinal abnormality and a physiological characteristic of increased mean artery-to-vein ratio (page 17, lines 9-12 of the final Office action mailed August 18, 2010). However, Applicants note that Upton et al. did not investigate **retinal abnormalities**, but instead is directed to measurements of axonal projections in **brainstem nuclei** (superior colliculus and lateral geniculate) originating from the retinal ganglion cells in knock-out mice as compared to wild type mice. **The superior colficulus and the lateral geniculate are not in the eye; they are located in the brainstem.** Thus, although axonal projections to the superior colliculus and the lateral geniculate are clearly of importance to vision, it is not clear how the Upton et al. might relate to a phenotype of eye abnormality, nor to a physiological characteristic of increased mean artery-to-vein ratio. As Upton et al. do not discuss retinal abnormalities, it is unclear how Upton et al. relates to the present claimed invention.

More particularly, Applicants disclose the results of the ophthalmologic measurements

(A/V ratio determined from optic fundus photography and angiography) taken from wild-type and knock-out mice having a disruption of the gene encoding PRO224, disclose that these results show differences between the wild-type and knock-out mice, and disclose that an abnormal A/V ratio is indicative of diseases or disorders such as ocular diseases corresponding to ophthalmologic disorders (page 163, lines 29-21). In addition, Applicants note that the results disclosed the present application demonstrate a difference in the mean artery-to-vein ratio **in the retinas** of knock-out mice as compared to gender-matched control wild-type mice. These observed differences therefore show that the retinas of knock-out mice are abnormal as compared to normal control mice. Thus, by definition, the observed differences are **retinal abnormalities** in the knock-out mice."

The following scope of enablement rejection is necessitated by claim amended filed on 10/29/2010 by Applicant.

Scope of Enablement

7. Claims 272, 273, 280-284, and 291 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying an agent that modulates an eye abnormality, the method comprising: (a) providing a transgenic mouse whose genome comprises a knockout of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the transgenic mouse of (a), wherein the transgenic mouse exhibits the following physiological characteristic compared with gender-matched wild-type littermates: an increased mean artery-to-vein ratio in the retinas; (c) administering a test agent to the transgenic mouse of (a); and (d) determining whether the test agent modulates said increased mean artery-to-vein ratio in the retinas of the transgenic mouse, whereby an agent which is determined to modulate said increased mean artery-to-vein ratio in

the retinas of the transgenic mouse is identified**, does not** reasonably provide enablement for the claimed methods for **(1)** any disruption of the gene which encodes for the native sequence PRO224 polypeptide other than a knockout of the gene which encodes for the native sequence PRO224 polypeptide, or **(2)** any physiological characteristic of eye abnormalities consistent with or associated with any disease other than an increased mean artery-to-vein ratio in the retinas. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The basis of this scope of enablement rejection is that (1) a disruption of a gene encompasses any frame-shrift mutation, any in-frame addition, deletion, and any truncation that do not result in complete loss of gene function (i.e. knockout), and (2) the increased mean artery-to-vein ratio in the retinas is the only disclosed physiological characteristic of eye abnormalities exhibited by the DNA33221-1133 (+/-) and (-/-) knockout mouse (notes: mouse DNA33221-1133 gene encoding PRO224 polypeptides).

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

The nature of the invention is directed to a method of identifying an agent that modulates an eye abnormality, the method comprising: (a) providing a transgenic mouse whose genome comprises a disruption of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the transgenic mouse of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type mouse, wherein the physiological characteristic of an eye of the transgenic mouse that differs from the physiological characteristic of the wild-type mouse is identified as an eye abnormality resulting from the gene disruption in the transgenic mouse; (d) administering a test agent to the transgenic mouse of (a); and (e) determining whether the test agent modulates said eye abnormality, whereby an agent which is determined to modulate an eye abnormality is identified.

The breadth of the invention encompasses a method of identifying an agent that modulates an eye abnormality, the method comprising: (a) providing a transgenic mouse whose genome comprises any disruption of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring any physiological characteristic of an eye of the transgenic mouse of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type mouse, wherein the physiological characteristic of an eye of the transgenic mouse that differs from the physiological characteristic of the wild-type mouse is identified as any eye abnormality resulting from the gene disruption in the transgenic mouse; (d) administering a test

agent to the transgenic mouse of (a); and (e) determining whether the test agent modulates said eye abnormality, whereby an agent which is determined to modulate an eye abnormality is identified.

With regard to gene encoding PRO224 polypeptide, the specification discloses isolation of a nucleotide sequence (SEQ ID NO: 1) that encodes a human PR0224 polypeptide (SEQ ID No: 2) from an unknown human cell type (See paragraphs [0230], US 2007/0292438, publication of instant application).

With regard to any phenotype and/or any physiological characteristic of any eye abnormality of a transgenic mouse, the specification discloses that in knockout mouse experiments, the mouse gene encoding PRO224 polypeptides (designated as DNA33221-1133) [UNQ198] was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_019421 or Mus musculus hypothetical protein 425018-1, protein reference: NP_062294 or hypothetical protein 425018-1; putative VLDL lipoprotein receptor precursor; DNA segment, Chr 17, ERATO Doi 716, expressed [Mus musculus]; the human gene sequence reference: BC007083 or Homo sapiens, 8D6 antigen, clone MGC: 14623 IMAGE: 4076237; the human protein sequence corresponds to reference: NP_057663 or 8D6 antigen (Homo sapiens) (See paragraphs [0669] and [0700], US 2007/0292438, publication of instant application). The specification discloses phenotypic Analysis (for Disrupted Gene: DNA33221-1133 (UNQ198) as follows: Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999;

5:22). Intra-peritoneal injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct opthalmological changes, this test can detect retinal changes associated with systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye (See paragraphs [0708], US 2007/0292438, publication of instant application). Ophthalmology analysis was performed on generated F2 wild type, heterozygous, and homozygous mutant progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according to the fundus images with Kowa COMIT+ software. This test takes color photographs through a dilated pupil: the images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). The specification states that many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wildtype (+/+) littermates would be indicative of such pathological conditions (See paragraphs [0709], US 2007/0292438, publication of instant application). The specification discloses the Results as follow: In this study, the (-/-) and (+/-) mice exhibited an increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates indicating retinal degeneration. The specification states that, in summary, by knocking out the gene identified as DNA33221-1133 encoding PRO224

polypeptides, both heterozygous and homozygous mutant progeny exhibit phenotypes which are associated with retinal degeneration. Such detected retinal changes are most commonly associated with cardiovascular systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to opthalmological disorders such as retinal degeneration. Thus, antagonists of PRO224 encoding genes would lead to similar pathological retinal changes, whereas agonists would be useful as therapeutic agents in the treatment of hypertension, atherosclerosis or other opthamological disorders including retinal degeneration and diseases associated with this condition (as indicated above) (See paragraphs [0710], Example 18, US 2007/0292438, publication of instant application).

It is worth noting that the claimed methods require "identifying an agent that modulates a phenotype associated with disruption of the gene that encodes for a PRO224". However, the specification does not provide any information regarding any agent that can reverse/modulate the increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates exhibited by the (-/-) and (+/-) mice, which Applicant asserts to be an indication of and/or associated with retinal degeneration. Pertaining to this issue, it is worth noting that the status of art indicates that there is no clear association, as Applicant asserts, between a phenotype of retinal abnormality (retinal degeneration) and a physiological characteristic of increased mean artery-to-vein (A/V) ratio.

Relevant to the statements documented in the preceding paragraph, the Examiner acknowledges that in the reply filed by Applicant on 10/29/2010, Applicant states that "Applicants disclose the results of the ophthalmologic measurements (A/V ratio determined from

optic fundus photography and angiography) taken from wild-type and knock-out mice having a disruption of the gene encoding PRO224, disclose that these results show differences between the wild-type and knock-out mice, and disclose that an abnormal A/V ratio is indicative of diseases or disorders such as ocular diseases corresponding to ophthalmologic disorders (page 163, lines 29-21). In addition, Applicants note that the results disclosed the present application demonstrate a difference in the mean artery-to-vein ratio **in the retinas** of knock-out mice as compared to gender-matched control wild-type mice. These observed differences therefore show that the retinas of knock-out mice are abnormal as compared to normal control mice. Thus, by definition, the observed differences are **retinal abnormalities** in the knock-out mice."

As stated in the beginning of this scope of enablement rejection, the basis of this scope of enablement rejection is that (**1**) a disruption of a gene encompasses any frame-shrift mutation, any in-frame addition, deletion, and any truncation that do not result in complete loss of gene function (i.e. knockout), and (**2**) the increased mean artery-to-vein ratio in the retinas is the only disclosed physiological characteristic of eye abnormalities exhibited by the DNA33221-1133 (+/-) and (-/-) knockout mouse (notes: mouse DNA33221-1133 gene encoding PRO224 polypeptides). Taking into consideration the claim amendments and Applicant's arguments filed on 10/29/2010, the specification **does not** reasonably provide enablement for the claimed methods for (**1**) any disruption of the gene which encodes for the native sequence PRO224 polypeptide other than a knockout of the gene which encodes for the native sequence PRO224 polypeptide, or (**2**) any physiological characteristic of eye abnormalities consistent with or associated with any disease other than an increased mean artery-to-vein ratio in the retinas.

(1) It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) should be removed from or added to a polypeptide's sequence and result in total loss of activity or result in destabilization of the protein is extremely complex, and well outside the realm of routine experimentation. In this regard, it is unpredictable whether any disruption of the gene which encodes for the native sequence PRO224 polypeptide in mouse would exhibit the same effect as a null mutation (i.e. a knockout, a complete loss of gene function). The specification does not disclose any structure-and-function analysis of mouse gene encoding PRO224 polypeptide. In the art, **Skolnick et al.** states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (See abstract, Skolnick et al., From genes to protein structure and function: novel applications of computational approaches in the genomic era, Trends in Biotechnol. 18(1):34-39, 2000). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2).

(2) The status of art at the time of filing as well as at present indicates that the phenotype of transgenic mouse is unpredictable. **Matthaei** teaches that although genetic manipulations in mice have provided a powerful tool for investigating gene function in vivo, recent studies have uncovered a number of developmental phenomena that complicate the attribution of phenotype

to the specific genetic change. Matthaei further teaches further complications in interpretation due to unexpected epigenetic effects involving transfer of RNA or protein in oocytes or sperm (See abstract, Matthaei, Genetically manipulated mice: a powerful tool with unsuspected caveats. J Physiol. 582(Pt 2):481-8, 2007). Matthaei teaches that the site at which the DNA is integrated is random, as are the number of copies of the transgene. Although the expression of the construct is faithful for the promoter, on many occasions it may also be significantly influenced by the local environment at the integration site (the 'position' effect). This can lead to the promiscuous expression of the transgene (often referred to as 'leakiness'), due to modification of the specificity of the promoter, or at times to a more severe phenotype, due to disruption of an unknown gene by insertion of the transgene (insertional mutagenesis). Furthermore, Matthaei teaches that a number of different 'founder' animals with different copy numbers and different integration sites must therefore be assessed in order to determine the correct/faithful expression of each transgene, and surprisingly, in one example, 24 different founders resulted in 24 different expression patterns making it impossible to determine which pattern was correct (See right column, page 481, J Physiol. 582(Pt 2):481-8, 2007).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention commensurate in scope with the claims 272, 273, 280-284, and 291.

Conclusion

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632